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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/096,589	06/12/1998	ROBERT J. SCHNEIDER	5914-65	1985

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PENNIE AND EDMONDS
1155 AVENUE OF THE AMERICAS
NEW YORK, NY 100362711

EXAMINER	
PROUTY, REBECCA E	
ART UNIT	**PAPER NUMBER**
1652	21

DATE MAILED: 07/15/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/096,589	Schneider et al.
Examiner	**Art Unit**
Rebecca Prouty	1652

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Apr 22, 2003*.

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *47-54* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *47-54* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Claims 1-46 have been canceled. Claims 47-50 and newly presented claims 51-54 are still at issue and are present for examination.

Applicants' arguments filed on 4-22-03, paper No. 20, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claims 47-50 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 47 (upon which Claims 49-50 depend) is indefinite in the recitation of "Src kinase activity that is enhanced relative to a patient not infected with HBV" as the levels of Src kinase activity in two separate patients (one infected with HBV and one not infected) are influenced by many different factors which cannot be controlled for as two individuals are never the same in all respects. As such one cannot determine the level of Src kinase activity enhancement that results from HBV infection and the scope of compounds recited in the claim is unclear. For purposes of examination it is assumed that the claim encompasses the administration to HBV infected patients of compounds which

inhibit Src kinase activity that is enhanced in an HBV infected cell relative to an identical cell not infected with HBV.

Claim 48 (upon which Claims 49-50 depend) is indefinite in the recitation of "Src kinase activity that is enhanced relative to a cell not infected with HBV" as it is not clear that the uninfected cell is identical to the infected cell except for the presence of the HBV infection. It is suggested that the claim be amended to recite "Src kinase activity that is enhanced relative to an identical cell not infected with HBV".

Claims 47-54 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The rejection is explained in the previous Office Action.

Applicants argue that the specification describes numerous compounds that can be used in accordance with the invention and specifically describes tyrosine kinase inhibitors including Csk, tryphostin derivatives, benzylidenemalonitrile derivatives, pyrazolopyrimidine derivatives, angelmicin B and small phosphotyrosine peptides. This is not persuasive because the specification describes all of these as examples of Src kinase

inhibitors and **not** examples of inhibitors of Src kinase activation as induced by HBV and/or HBx. As such the specification does not describe these compounds as species within the currently claimed genus of compounds. While as noted by applicants response it was known in the art that one mechanism of Src kinase activation was the dephosphorylation of Y527 and/or the phosphorylation of Y416, there is no showing in the specification that HBV activation of Src kinase is achieved by either or both of these mechanisms and it is unclear what if any tyrosine kinase/tyrosine phosphatase should be inhibited in order to produce inhibition of Src kinase activation induced by HBV and/or HBx. It should be noted that any of the above tyrosine kinase inhibitors which lack activity against the Src kinase itself might act as activators of HBV infection and replication (if they inhibit phosphorylation of the kinase which phosphorylates Y527) or inhibitors (if they inhibit the kinase which phosphorylates Y416) or have unpredictable effects (if they inhibit both the phosphorylation of Y527 and Y416). As the mechanism of HBV activation of Src kinase was not known in the art nor described in the specification, one of skill in the art would not have been in possession of knowledge of even a single compound which clearly falls within the scope of the currently

claimed genus. Applicants submission of references teaching that HBx activates Pyk2 which in turn activates Src kinase is not persuasive because the showing that HBx activates Pyk2 was published well after the filing date of the instant application. Description of the invention must have been present in the original application and not depend on later disclosed information. The specification describes explicitly only that tyrosine kinase inhibitors which inhibit Src tyrosine kinase activity (i.e., non-elected subject matter) will inhibit HBV infection and replication, and fails to provide sufficient disclosure for one of skill in the art to predict what if any effect other tyrosine kinase inhibitors will have on HBV infection and replication. As such the specification does not provide sufficient description of members of the genus **such as** by structure, formula, chemical name or physical properties such that one skilled in the art can visualize or recognize the identity of the members of the genus.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 47-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Moriya et al.

Moriya et al. teach the inhibition of HBx gene transcription and translation and hepatocellular carcinoma (HCC) by administration of HBx antisense oligonucleotides. While Moriya et al. do not show that these oligonucleotides inhibit activation of Src kinase, this is an inherent effect of the antisense oligonucleotide of Moriya et al. as the oligonucleotide of Moriya inhibited HBx expression such that there is no HBx present to activate Src kinase (see Figures 1 and 2). Moriya et al. do not treat a patient or cell infected with HBV with the antisense oligonucleotides. However, Moriya et al. explicitly suggest that the antisense oligonucleotide would be useful for the inhibition of HBV replication as HBx is considered to be indispensable in establishing infection and regulating viral replication. Therefore, it would have been obvious to one of ordinary skill in the art to treat an HBV infected patient or cell with the

antisense oligonucleotide of Moriya et al. in order to inhibit HBV replication.

Applicants argue that the examiner is improperly using inherency in a 103 rejection. This is not persuasive because the limitation of "that inhibits Src kinase activity ..." merely defines what compounds are being administered by the claimed methods and in no way limits the steps of the method at all. Moriya et al. explicitly suggests doing every step of the claimed method, i.e. administering a HBx antisense oligonucleotide to an HBV infected patient. Knowledge of how this compound acts *in vivo* is not necessary for either motivation to do all the claimed steps (clearly present in view of the explicit suggestion of Moriya et al.) nor for a reasonable expectation of success in view of the successful prevention of HBx gene expression in the mouse model system. Applicants statement that Moriya suggests only the use of HBx antisense oligonucleotides as a method of preventing hepatocellular carcinoma in HBV infection and not as a means of inhibiting HBV infection/replication is incorrect. Moriya states on page 222:

> Since the HBx gene is considered to be indispensable for the establishment of woodchuck hepatitis virus infection and to regulate the viral replication by its transactivating function, the antisense sequence described in this study may also **be effective in the inhibition of HBV replication**" [emphasis added]

This clearly suggests using the antisense oligonucleotide as a means of inhibiting HBV infection/replication. Furthermore, it should be noted that Moriya et al. further suggests that other small molecules which inhibit HBx protein would be useful also (see last sentence on page 222). Finally applicants argue that the antisense oligonucleotide does not meet the requirement that the compound used be "capable of inhibiting HBx-mediated Src kinase activity in a cell-based assay". First it should be noted that no such limitation is present in claims 47 and 48. Second the antisense oligonucleotide would be identified in a cell based assay in which the Src kinase activity in a cell transformed with an expression vector encoding HBx was compared in the presence and absence of the antisense oligonucleotide. This appears to be the assay recited in Claims 49 and 53. Applicants statement that the "applicant's discovery that HBx activated the Src kinase signaling pathway during HBV infection/replication was the first suggestion of a cellular target that could effect HBV inhibition" is highly misleading as the only cellular target suggested is in fact Src kinase itself as the pathway between HBx and Src is not disclosed and inhibitors of Src kinase are not the subject mater of the instant claims.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rebecca Prouty, Ph.D. whose telephone number is (703) 308-4000. The examiner can normally be reached on Monday-Friday from 8:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy, can be reached at (703) 308-3804. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Rebecca Prouty
Primary Examiner
Art Unit 1652